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Perspective Piece

What Historical Records Teach Us about the Discovery of Quinine

Louis H. Miller,[1]* Jesus Rojas-Jaimes,[2] Leanne M. Low,[1] and Gilberto Corbellini[3]

[1]*Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland;* [2]*Faculty of Health Sciences, Universidad Privada del Norte, Lima, Peru;* [3]*Museum of History of Medicine, Sapienza University of Rome, Rome, Lazio, Italy*

Abstract. The origin of quinine from Peru remains a mystery because of the lack of primary data—in particular, those produced by the Jesuits working in Peru. The discovery of cinchona bark and its use in malaria treatment must have come from the Jesuits, who worked with the native Andeans, the Quichuan people, and learned how the bark of the cinchona tree could be used for chills. Unknown is whether the Andean people used it for fever that may have been the result of malaria. We explored the literature of the 1600s, 1700s, and later to trace the history of quinine that is available. All these secondary sources lack the primary data of the Jesuits in their work with native Andeans, nor is there information on how the discovery of its use for malaria-like fevers came about. One clue comes from the Jesuits who talked with the Andean people and learned about quinine. But was it used for fever? Why did the Jesuits test it against (tertian or quartan) fevers that could have been the result of malaria? The gap in our knowledge can only be resolved with the discovery of written documents by the Jesuits about quinine for malaria.

In 2005, I (L. H. M.) was at the International Conference on Parasitology and Vector Biology in Shanghai, China, and I asked everyone there: Who discovered the herbal antimalarial drug artemisinin? No one knew! My curiosity was based on how little we knew about the discovery of quinine in the 1600s. Su and I[1] began the study of the origin of artemisinin, which led to our identification of Tu Youyou and her central role in this discovery. This drug was extracted from *Artemisia annua*, as described by Ge Hong (283–243 CE) in China, and his writings led Tu Youyou to its discovery in the modern era. Interestingly, Carl Linnaeus was told by the father of his future wife that he could not marry his daughter until he had a degree. He discussed, at the University of Harderwijk in 1735, a thesis on the cause of malaria and took his medical degree.[2] Although he was completely wrong about the cause of the disease, which he attributed to particles of clay that had been dissolved in the drinking water, he correctly identified two treatments that were quina bark (*Cinchona officinalis*) and *Artemisia annua*.[3] How did he know about *Artemisia annua?* The knowledge must have been introduced into Europe by the Chinese pharmacopeia from travelers such as Marco Polo, who were returning from China.

Quinine, extracted from the bark of the cinchona tree (Figure 1), is one of the greatest discoveries of all time in herbal medicine, and was one of the few drugs in William Osler's armamentarium for medicine. Today, we do not know who discovered the use of cinchona for malaria. There is no question that the drug was used by native Andeans for medicinal purposes, but did they use it to cure malarial fevers? The important question that remains is: What did the Jesuits learn from the Andean people that may have led them to treat malaria with cinchona bark? There is common lore that quinine was used to treat the Countess of Chinchon (the wife of the Viceroy of Peru) for malaria, but this lore is fantasy.[4] Research conducted by Alberto Bailetti[5] about the life of the Jesuit Augustine Salumbrino in Lima during the early decades of the 17th century found that it was the Viceroy of Peru, in early May 1631, who fell ill with malaria and was cured by the administration of cinchona bark powder.

Did the Jesuits test the extract of the bark of the cinchona tree against malaria? To answer this question, we need primary data written by the Jesuits themselves. Hopefully, documents that were written by the Jesuits exist but remain undiscovered and unstudied from the period after 1600. It is often said that the native Andeans, the Quichuan people, could not have discovered quinine as an antimalarial, but we simply do not know if this is true. Until we understand the history of the cultural exchanges between the native Andeans and the Jesuits, the origins of quinine as an antimalarial chemotherapy will remain a mystery. Seeking to answer this question will surely open an amazing new field in the history of medicine.

The most likely theses circulating on the origin of cinchona bark as a cure—aside from legends such as the curing of the Countess of Chinchon,[4] pumas seen drinking in a lake and being cured of shivering, or the earthquake that caused cinchona trees to fall into a lake whose waters became therapeutic—concern the use of the bark to treat cold and dampness or the observation of the treatment of malaria sufferers by Andean shamans. Some authors, such as Francisco Guerra,[6,7] denied that malaria was present in South America and that shamans used cinchona bark as their natural medicine. Historian Matthew James Crawford[8] takes a different view, claiming—on the basis of ethnobotanical data and the Andean healers' medical cosmogony—that cinchona bark was part of the traditional native healer's armory of treatments and that the ecosystem in which the plant grew made it conceivable as a febrifuge. The Loja region in Ecuador was an important center of traditional medical knowledge, and Crawford argues that the African slave trade to South America initiated by the Portuguese in the early decades of the 16th century transferred the malarial parasites to the New World. The local healers, with at least more than a century of circulation of the *Plasmodium* spp., were able to test and observe the effects of cinchona bark in the area where they practiced, and taught its use to Europeans, particularly the Jesuits, whose presence in the region date

*Address correspondence to Louis H. Miller, Twinbrook 3, Room 3E-32D, 12735 Twinbrook Pkwy., Rockville, MD 20852. E-mail: lmiller@niaid.nih.gov

FIGURE 1. *Cinchona officinalis*, the tree from which quinine is derived. **(A)** A closeup of a branch of *C. officinalis* (permission to reproduce received from Mirbel Epiquién Rivera). (**B**) A cinchona tree growing in the landscape of Pajal, Huancabamba, Piura, Peru (permission to reproduce received from Mirbel Epiquién Rivera). (**C**) The National Shield of Peru is found on the Peruvian Flag (free image from https://www.fap.mil.pe/index.phpo/nosotros/escudo-nacional). It has the cinchona tree as an indication of its importance to Peruvian history. (**D**) The case of a machine for crushing cinchona bark used in the Santo Spirito Hospital's pharmacy in the mid-17th century (permission to reprint from Dr. Gaspare Baggieri, Curator, Museo Nazionale dell'Arte Sanitaria, Lungotevere in Sassia 3, 00186 Roma, Italy).

back to 1568,[9] in tow of the conquistadors, and who were interested in native knowledge besides converting so-called savages. Molecular studies confirm that malarial parasites began arriving in the Americas from Africa in the middle of the 16th century.[10] It has also been documented that by the mid-1580s, a massive influx of slaves into the city of Lima probably consolidated the presence of *Plasmodium falciparum*. By the early 17th century, 40% of Lima's population was of African descent, coming from Cartagena and Panama, with Africans or Afro-Peruvians outnumbering Spaniards, the latter of which comprised less than 38% of the inhabitants. The percentage reflected in the census would have been greater had slaves living in estates that surrounded Lima been counted.[11,12]

In the early 1630s, the Augustinian friar Antonio de la Calancha, of Andean descent and familiar with the medical

practices of the local people, wrote, "A tree grows in the country of [Loja] which is used for fevers, whose bark, of cinnamon colour, made into powder given to the weight of two reals of silver in a drink, cures the ague and tertians; it has produced in Lima miraculous results."[13] In turn, Gaspar Caldera de la Heredia, a doctor in Seville – a center of importation from the West Indies – wrote in 1663 about cinchona in *Tribunalis Illustrationes et Observationes Practicae*, stating that it is a tree called *quarango* by the natives who use it as timber. According to Caldera, Jesuits in the missions at the foot of the mountains were said to have noticed that the natives drank the powdered bark in hot water after being exposed to humidity and cold.[14] Noting the effect on chills, a symptom also recorded with the quartan and tertian fevers of malaria, the Jesuits also tested it on some patients with fever. The bark was allegedly given to Gabriel de Espana, a pharmacist in Lima, who then distributed it to doctors.[15,16]

Gaspar Bravo de Sobremonte, a doctor from Valladolid, wrote in 1669, in *Disputatio Apologetica pro Dogmatica Medicine Praestantia*,[17] that the bark was used after Peruvians had been observed to drink it pulverized in water to treat cold chills. Diego Salado Garzés, who was in charge of studying new medicines at the University of Seville, reiterates the same concept in his *Estaciones Medicas* of 1678 and 1679:

> *[T]the missionaries of the Society of Jesus [in the province of Quito] used the powders of Quarango following the second transit of Galen with great ingenuity, after observing that the Indians took them when shivering from cold after swimming in iced water or from the coldness of the snow and stopped trembling within a short time. The Jesuits used them to control the shivering in tertian and quartan fevers; and as they noticed that the repetition of the fever stops, they advised them as a great febrifuge to cure them.*[18]

The numerous pamphlets that were produced between 1638 and 1705 discuss the origins, efficacy, and use of bark powder in Spain and are examined in *Guerras Panfletarias en Torno a la Quina* by Mar Rey Bueno.[16]

Comparatively reviewing the literature, Honigsbaum and Willcox[19] thought that the bark was used traditionally by native healers in the context of a medical practice that mainly resorted to the side effects of quinine, because the febrifuge effects were exerted only against malarial fevers. When malaria parasites made their appearance by way of the Portuguese and Spaniards in the slave trade from Africa, as was the case with the Yanomami of the Brazilian Amazon when malaria was introduced by gold miners in the 1980s, they empirically sought remedies in their natural pharmacopoeia, and Andean healers began experimenting with plants already in use for different purposes.[19]

The story of quinine's introduction into Europe has been told by Saul Jarcho,[20] and its first "empirical" experimentations by Gachelin et al.[21] There is at least some agreement among historians on two points[22]: the bark began to arrive in Europe in the late 1620s and early 1630s on its way to Spain and then Italy, and by 1647 it was arriving continuously in Rome, where it was prepared in powder form and sorted. The first official record of a prescription for Peruvian bark in Rome dates to the early 1630s by the Jesuit Domenico Anda, chief apothecary at the Hospital of Santo Spirito. It contains the first formal indication of cinchona as a component of a formula, in this case called *Corticus peruvianus*. Unfortunately, the original document is untraceable and only a reproduction is available thanks to a 1954 text by Pietro De Angelis.[23]

Archival research carried out by Fiammetta Rocco,[15] to write a valuable history of quinine, has brought to light the role of the Italian Jesuit Augustino Salumbrino in sending quinine to Rome. When Salumbrino arrived in Lima in 1605, he set up an efficient apothecary's shop, from which he distributed numerous medicinal plants, including Peruvian bark, to the Americas. Inventories drawn up by the Jesuit administrators of the College of San Pablo show that Salumbrino sent a quantity of cinchona to Rome through Father Alonso Maria Venegas in 1631. Venegas arrived in Rome in 1632 with the bark. Bailetti[5] documents that on the afternoon of May 31, 1631, a ship set sail from the port of Callao, embarking with Jesuit procurators Fathers Alonso Messia and Hernando León Garavito, who traveled with bales of powdered cinchona bark prepared by Augustino Salumbrino in the Jesuit apothecary's shop. The cargo arrived in Rome, destined for Santo Spirito Hospital, after 6 months and many vicissitudes.

Salumbrino is an interesting protagonist because he was a protégé of Carlo Borromeo, a very influential cardinal and archbishop of Milan from 1564 to 1584, whom he saw die of malaria contracted in Fall 1584 in the swampy, rice-growing areas of Novara. After first encountering malaria, he traveled to Rome in 1590 after the death of his patron, where he was a nurse and pharmacist at the Santo Spirito Hospital and where he could observe the tragic impact of intermittent fevers on the inhabitants of Rome and its environs routinely admitted to Santo Spirito.

According to Bailetti,[12] Salumbrino regularly distributed cinchona bark powder in Lima, and people suffering from malaria came to his spice shop. One of the recipes in use in the city, described as "very safe for the treatment of all kinds of tertiary and quartan diseases of which wonderful effects have always been experienced," consisted of a drink prepared with oranges, sugar, and water, which was boiled and then cooled, into which was poured

> *the amount of Cascarilla powder that is given in the spice shop, stirring the mixture until it is well incorporated . . . this drink is taken on an empty stomach, then stirring the mixture first, of which only four ounces of the drink is taken in a small glass, leaving the rest to be taken in the next two days if necessary. . . . [The drink can be taken] the same day as the fever, an hour or two, more or less, before the onset of chills.*[12]

The second evidence of the arrival of Peruvian bark at the spice house of the Ospedale di Santo Spirito dates from December 1649, when the Peruvian Jesuit Bartholomé Tafur, traveling to Rome for the election of the Jesuit leader, carried a quantity of bark in his luggage.[24] In 1646, 1650, and 1652, delegates to the 8th, 9th, and 10th general councils of the Jesuits Order (three from each province) returned to their homes carrying the bark with them, and at the same time there is evidence of its use in Jesuit colleges in Genoa, Lyon, Leuven, Regensburg, and those in Rome.[25]

We can take for granted the therapeutic value of cinchona bark against intermittent fevers, which were discovered to be caused by malaria parasites. But, controversies persisted at least until Francesco Torti's study was published in 1712, based on the recipe of the Jesuit friar Pietro Paolo Puccerini in 1649, known as *Schedula Romana*.[26] It is a simple leaflet illustrating the characteristics and dosage of the preparation. In fact, there is a lack of evidence of the steps that led Puccerini to conclude that the preparation based on Peruvian bark should be "taken for the quartan and tertian fevers that are accompanied by cold."[30] The apothecary Puccerini, who established a dosage practically equivalent in quinine content to what would be used after the isolation of the specific alkaloid, called it an "infallible" treatment. There can be no doubt about the impression made, because if that recipe was used to treat the summer–autumn fevers of the hundreds of people admitted to the Ospedale di Santo Spirito in Sassia, its efficacy would be evident, given that these fevers were nearly all from malaria.

In different geographic and sociocultural contexts, such as northern Europe, the uncertainties became greater. After the failure of the cure of Archduke Leopold William of Austria, Governor of Belgium and Burgundy, physician Joannes Jacobus Chifletus published *Exposure of the Febrifuge Powder from the American World* in 1653 in which he questioned the efficacy of the preparation, claiming that it simply lengthened the intervals between fevers, and caused putrefaction of the humours.[27] That same year, in Rome, the Jesuit and naturalist,[28] where he claimed that thousands of people had been cured in Rome and dismantled Chifletus' contradictions and prejudices in criticizing Peruvian bark. The controversy had several developments in Europe, and texts that were published for or against the use and effectiveness of the bark contained a great deal of information, but also misinformation, particularly on the botanical characteristics, which would complicate the use of the preparation in the decades to come.[16,29]

Honoratus Fabri[30] wrote that the Peruvian bark had been tested by Gabriele Fonseca, a Portuguese physician and the Pope's personal physician, at the request of Spanish Cardinal Juan de Lugo, who had been director of the apothecary's shop at the Ospedale di Santo Spirito in Rome since 1630. de Lugo, elevated to cardinal in 1643, had contracted malaria during the conclave of 1644, when one cardinal died and five fell ill, and had witnessed the tragic conclave of 1623, when Urban VIII was elected to be the Pope in the midst of a malarial outbreak that killed 5 cardinals and 40 conclave participants. Urban VIII himself fell ill. But when did the test take place? This is not known, and we know almost nothing about Gabriele Fonseca,[31] apart from the fact that in 1668 to 1672 he was portrayed by Lorenzo Bernini in a very famous marble bust, one of the best known and appreciated by historians of Baroque art.

Prominent in the discussion of the efficacy and origins of cinchona bark are the publications of Sebastiano Bado,[32] which were influential in circulating misleading information, such as the legend of the Countess of Chinchon and the exchange of a different plant for what would be recognized as cinchona.[29] Bado was a Genoese physician who practiced for a few years in Rome, frequenting the influential physician and philosopher Girolamo Bardi and, of course, Cardinal Juan de Lugo, both of the Order of Jesus. Returning to Genoa around 1655 to head the hospital of Pammantone, where he claimed to have first experimented there with bark to demonstrate its efficacy against quartan and tertian fevers,[33] Bado learned in 1659 of the circulation of counterfeit powders and discussed these issues in letters with de Lugo and other apothecaries and physicians.[31]

Imagine having no way to identify malaria and not knowing that quinine was sometimes contaminated by balsam, which has no effect on malaria.[29] Add to this the prejudice against a treatment described as Jesuit powder, one begins to appreciate why there was controversy about this great drug. The clearest picture of its value came from Francesco Torti in Italy who had studied fevers of all kinds.[20] He also argued that the myth that fever did not lead to death was wrong. Again, today we know that fever from *P. falciparum* causes death, of course. His treatise on fever and the effect of cinchona on curing some causes of fever is a classic in medicine.[20] Today we take it for granted that such medicine was miraculous in an era when few effective medicines existed. If you can picture working in this time, you can appreciate the challenges and the greatness of Torti and others[20,21] in arriving at the importance of this treatment that would, in the future, save large numbers of lives.

In addition to the natural product, quinine, the search for synthetic antimalarial drugs began with the structure of quinine solved by French scientists Pierre Pelletier and Joseph Caventou in 1820. Paul Erhlich began the work toward synthetic antimalarial drugs with the use of methylene blue because it stained malarial parasites.[34] Methylene blue's activity was less than that of quinine, and thus a sidechain was added to increase its activity. This sidechain became critical for the action of all drugs in this class.[35] An important advance was the discovery of a related 8-aminoquinoline with action against the dormant liver stages. No other class of drugs against these stages has been identified to date. This drug, primaquine, unfortunately causes hemolysis in glucose-6-phosphate dehydrogenase deficiency. The final discovery in the class of drugs was the 4-aminoquinolines, including chloroquine, against the blood stages of *Plasmodium* spp. that appeared to be the answer for eradication, until resistance occurred in Southeast Asia spread throughout Africa. Interestingly, quinine has remained effective against malaria to this day.

Today, we lack the primary data on the discovery of the bark of the cinchona tree as a treatment of malaria. The native Andeans had no written language, and the information must be derived from the Jesuits of that time. It is necessary for someone to trace the original Jesuit writings to gain further access to this medical mystery.

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Authors' addresses: Louis H. Miller and Leanne M. Low, Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, E-mails: louis.miller@nih.gov and leanne.low@nih.gov. Jesus Rojas-Jaimes,

Faculty of Health Sciences, Universidad Privada del Norte, Lima, Peru, E-mail: jesus.rojas.jaimes@gmail.com. Gilberto Corbellini, Museum of History of Medicine, Sapienza University of Rome, Rome, Lazio, Italy, E-mail: gilberto.corbellini@gmail.com.

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